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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Application of: Barney et al.

Application No.: 08/487,355

Group Art Unit: 1648

Filed: June 7, 1995

Examiner: Stucker, J.

For: METHODS FOR INHIBITION OF MEMBRANE-FUSION ASSOCIATED EVENTS, INCLUDING HEPATITIS B VIRUS TRANSMISSION

Attorney Docket No.: 7872-027

APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. §§ 1.191 AND 1.192

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BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to the provisions of 37 C.F.R. § 1.191 and § 1.192, an appeal is taken herein from the final rejection of Claims 16-19 of this application. Appellants submit an original and two copies of this appeal brief accompanied a Petition for Extension of Time (in duplicate) for five months from July 11, 1998 up to and including December 11, 1998. Appellants also submit herewith Exhibit A: an appendix of the claims pending and under appeal in this application.

In accordance with 37 C.F.R. § 1.17(c), it is estimated that the fee for filing this Brief on Appeal is $155.00 (Small Entity). Please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

I. REAL PARTY IN INTEREST

Appellants have assigned the entire right and interest in the instant application to Trimeris, Inc.

II. STATUS OF CLAIMS

Original Claims 1-8, 10-13 and 15 of this application were canceled upon filing of the application on June 7, 1995, leaving Claims 9 and 14 pending. Claim 14 was canceled in a Preliminary Amendment filed on August 27, 1996, and Claim 9 was amended in a Supplemental Preliminary Amendment filed on September 19, 1996. Claim 9 was canceled and new Claims 16-19 were added in an Amendment filed on July 28, 1997. Claims 17 and 19 were amended to include SEQ ID NOS. in an Amendment filed on September 12, 1997. Finally, in an Amendment filed on May 11, 1998, Claims 16, 18 and 19 were canceled, Claim 17 was further amended, and new Claims 20-55 were added.

In an Advisory Action mailed May 26, 1998, the Examiner indicated that the amendment filed under 37 C.F.R. § 1.116 on May 11, 1998 had been entered and that Claims 17 and 20-55 are pending and under final rejection. A copy of these pending claims is presented in the attached Exhibit A.

III. STATUS OF AMENDMENTS

As noted above, in an Advisory Action mailed on May 26, 1998, the Examiner indicated that the amendment filed under 37 C.F.R. § 1.116 on May 11, 1998 had been entered and that Claims 17 and 20-55 are pending and under final rejection. A copy of these claims is attached hereto as Exhibit A. Dependent Claims 20-55 recite individual sequences and/or specific embodiments of the functional groups "X" and "Z" recited in Claim 17. Thus, Applicants respectfully submit that upon a finding of allowability of Claim 17, Claims 20-55 should also be found allowable.

A Supplemental Amendment is concurrently being filed by Appellants canceling the original abstract of the application, and replacing it with a new abstract that accurately describes the claimed invention. Appellants submit that entry of this Amendment is proper in that the total effect of the amendment is to remove issues from appeal (M.P.E.P § 1207, Seventh Ed., July 1998).

IV. SUMMARY OF THE INVENTION

The present invention, as described and claimed, relates to methods of using peptides having an amino acid sequence of a region of a hepatitis B virus which correspond to domains of viral proteins discovered by Appellants, and referred to in the instant specification

as "DP178-like" and "DP107-like" domains. The peptides of the invention exhibit antiviral activity, believed to result from the inhibition of viral induced fusogenic events. The claims of the present invention are particularly drawn to methods of using these peptides to inhibit hepatitis B transmission to cells.

The peptides recited in the claims of the invention have an amino acid sequence of a region of hepatitis B surface antigen protein which is identified by one of the computer associated sequence search motifs of the invention -- ALLMOTI5, 107x178x4, or PLZIP. These search motifs successfully identify specific regions of proteins similar to DP107 and D178. The antiviral properties of these specific peptides are fully described an enabled, by means of routine assays which are described, *e.g.*, in Section 5.5, on page 334, line 30 through page 338, line 14 of the instant specification as originally filed.

The pending claims (*i.e.*, Claims 17 and 20-55) recite methods of using peptides having the specific amino acid sequences recited within the claims to inhibit transmission of hepatitis B. Each of the recited peptides is demonstrated to inhibit hepatitis B virus transmission, as shown in the working example presented in Section 22, page 390, line 20 through page 391, line 21.

V. ISSUES

The following issue is presented for review in this appeal:

Whether the method recited in Claim 17 is enabled within the meaning of 35 U.S.C. § 112, first paragraph. The Examiner contends that the method is not enabled because, the Examiner contends, the instant specification as originally filed, although enabling for *in vitro* methods, is not enabling for *in vivo* methods. This rejection is error, and should be reversed for the reasons discussed below.

VI. ARGUMENTS

THE METHOD OF CLAIM 17 IS FULLY ENABLED WITHIN THE MEANING OF 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 17, drawn to methods of using specific peptides to inhibit hepatitis B virus transmission to a cell, has been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In the Advisory Action mailed on May 26, 1998, the Examiner has maintained the rejection based on the contention that the claimed methods, although enabled *in vitro*, are

not enabled *in vivo*. In particular, the Examiner contends that the instant specification does not describe any correlation between the *in vitro* models relied upon to demonstrate anti-viral activities, and the scope of the invention as claimed.

At the outset, Applicants again point out that Claim 17 recites methods for using *specific* peptides recited in the claim to inhibit transmission of hepatitis B virus to cells. Each of the recited peptides has an amino acid sequence of a region of hepatitis B surface antigen protein which is defined by one of the computer associated sequence search motifs of the invention shown to successfully identify peptides which exhibit potent antiviral activity (see, in particular, Section 22, page 390, line 20 through page 391, line 21). In particular, these peptides are shown to *inhibit viral infection to cells* through routine assays that are well known to those skilled in the art and are described, *e.g.*, in Section 5.5, on page 334, line 30 through page 338, line 14, as well as by working examples, including the Example in Section 22, on page 390, line 20 through page 391, line 21, which describes the use of such assays to characterize the antiviral activity of the recited hepatitis B virus peptides.

Contrary to the Examiner's contentions, the *in vitro* assays discussed in the application do, indeed, reflect anti-viral activity *in vivo*, including inhibition of viral transmission to cells. In particular, Section 6 (page 356, line 25 through page 363, line 5) of the instant specification as originally filed demonstrates that DP178 has potent anti-viral activity in the same *in vitro* assays as those taught in Section 22 of the specification for determining the anti-hepatitis B activity of the peptides recited in Claim 17. DP178 is also known to exhibit anti-HIV activity and inhibit transmission of HIV *in vivo*, as assayed by the HuPBMC-SCID mouse model, and by human clinical trials. Thus, the *in vitro* assay in Section 6 of the instant specification correlates well with the anti-HIV activity of DP178 *in vivo*.

The peptides recited in the pending claims of the instant application are specific DP178- and DP107-*like* peptides having an amino acid sequence of a region of the hepatitis B surface antigen protein identified by one of the computer associated sequence search motifs of the invention -- ALLMOTI5, 107x178x4, or PLZIP. Anti-hepatitis B activity of these peptides is exhibit to result from the same mechanism as the anti-HIV activity of DP178, namely the peptides' inhibition of viral-induced fusogenic events. Thus, Applicants submit that the *in vitro* cell fusion assays taught in Section 22 of the instant specification do, ineed, predict anti-HepB activity of the same peptides (*i.e.*, of the DP178- and DP107-like hepatitis

B proteins recited in Claim 17) *in vivo*, including the inhibition of transmission of hepatitis B virus to cells.

Thus, as discussed in detail above, the peptides recited in Claim 17 are fully enabled, within the meaning of 35 U.S.C. § 112, first paragraph. In particular, the instant specification provides assays which demonstrate the anti-viral activity of the recited peptides. Further, as explained above, one skilled in the art can readily appreciate that these assays correlate with the anti-viral activity of the recited peptides *in vivo*. Thus, the specification as originally filed enables the skilled artisan to practice the claimed methods *in vivo* as well as *in vitro*. In view of the foregoing, the rejection under 35 U.S.C. § 112, first paragraph, should be reversed.

VII. CONCLUSIONS

For the reasons set forth above, Appellants respectfully request that the rejection of the claim on appeal under 35 U.S.C. § 112, first paragraph, and the objection to the abstract of the instant specification be reversed.

Respectfully submitted,

Date December 11, 1998

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Enclosure

EXHIBIT A: APPENDIX TO APPELLANTS' BRIEF ON APPEAL

CLAIMS ON APPEAL
Serial No. 08/487,355
Attorney Docket No. 7872-027

17. A method for the inhibition of transmission of a hepatitis B virus to a cell, comprising contacting the cell with an effective concentration of a peptide having the formula:

X-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGGTTVCLGQNSQSP-Z;
X-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-Z;
X-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-Z;
X-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-Z;
X-LQAGFFLLTRILTIPQSLDSWWTSLNGLGGTTVCL-Z;
X-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-Z;
X-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-Z;
X-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-Z;
X-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-Z;
X-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-Z;
X-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-Z;
X-PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGCRTCMTT-Z;
X-PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGML-Z;
X-GYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLP-Z
X-YRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPV-Z;
X-RWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVC-Z;
X-WMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCP-Z;
X-MCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPI-Z;
X-CLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLI-Z;
X-LRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIP-Z;
X-RRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPG-Z;
X-RFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGS-Z;
X-FIIFLFILLLCLIFLLVLLDYQGMLPVCPLIGGSS-Z;
X-IIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSST-Z;
X-IFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTS-Z;
X-FLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTST-Z;
X-LFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTG-Z;
X-FILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGP-Z;
X-ILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPC-Z;
X-LLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCR-Z;
X-LLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRT-Z;
X-LCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTC-Z;
X-CLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTCM-Z;
X-LIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTCMT-Z; or
X-IFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTCMTT-Z;
(SEQ ID NOS: 239-273, respectively)

in which:

amino acid residues are presented by the single-letter code;

X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecule carrier group;

Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group for an effective period of time so that no infection of the cell by the virus occurs.

20. The method of Claim 17 wherein the peptide has the formula

X-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGGTTVCLGQNSQSP-Z (SEQ ID NO: 239).

21. The method of Claim 17 wherein the peptide has the formula

X-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-Z (SEQ ID NO: 240).

22. The method of Claim 17 wherein the peptide has the formula

X-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-Z (SEQ ID NO: 241).

23. The method of Claim 17 wherein the peptide has the formula

X-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-Z (SEQ ID NO: 242).

24. The method of Claim 17 wherein the peptide has the formula

X-LQAGFFLLTRILTIPQSLDSWWTSLNGLGGTTVCL-Z (SEQ ID NO: 243).

25. The method of Claim 17 wherein the peptide has the formula

X-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-Z (SEQ ID NO: 244).

26. The method of Claim 17 wherein the peptide has the formula

X-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-Z (SEQ ID NO: 245).

27. The method of Claim 17 wherein the peptide has the formula

X-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-Z (SEQ ID NO: 246).

28. The method of Claim 17 wherein the peptide has the formula

X-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-Z (SEQ ID NO: 247).

29. The method of Claim 17 wherein the peptide has the formula

X-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-Z (SEQ ID NO: 248).

30. The method of Claim 17 wherein the peptide has the formula

X-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-Z (SEQ ID NO: 249).

31. The method of Claim 17 wherein the peptide has the formula

X-PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTG PCRTCMTT-Z (SEQ ID NO: 250).

32. The method of Claim 17 wherein the peptide has the formula

X-PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGML-Z (SEQ ID NO: 251).

33. The method of Claim 17 wherein the peptide has the formula

X-GYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLP-Z (SEQ ID NO: 252).

34. The method of Claim 17 wherein the peptide has the formula X-YRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPV-Z (SEQ ID NO: 253).

35. The method of Claim 17 wherein the peptide has the formula X-RWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVC-Z (SEQ ID NO: 254).

36. The method of Claim 17 wherein the peptide has the formula X-WMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCP-Z (SEQ ID NO: 255).

37. The method of Claim 17 wherein the peptide has the formula X-MCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPI-Z (SEQ ID NO: 256).

38. The method of Claim 17 wherein the peptide has the formula X-CLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLI-Z (SEQ ID NO: 257).

39. The method of Claim 17 wherein the peptide has the formula X-LRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIP-Z (SEQ ID NO: 258).

40. The method of Claim 17 wherein the peptide has the formula X-RRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPG-Z (SEQ ID NO: 259).

41. The method of Claim 17 wherein the peptide has the formula X-RFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGS-Z (SEQ ID NO: 260).

42. The method of Claim 17 wherein the peptide has the formula

X-FIIFLFILLLCLIFLLVLLDYQGMLPVCPLIGGSS-Z (SEQ ID NO: 261).

43. The method of Claim 17 wherein the peptide has the formula

X-IIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSST-Z (SEQ ID NO: 262).

44. The method of Claim 17 wherein the peptide has the formula

X-IFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTS-Z (SEQ ID NO: 263).

45. The method of Claim 17 wherein the peptide has the formula

X-FLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTST-Z (SEQ ID NO: 264).

46. The method of Claim 17 wherein the peptide has the formula

X-LFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTG-Z (SEQ ID NO: 265).

47. The method of Claim 17 wherein the peptide has the formula

X-FILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGP-Z (SEQ ID NO: 266).

48. The method of Claim 17 wherein the peptide has the formula

X-ILLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPC-Z (SEQ ID NO: 267).

49. The method of Claim 17 wherein the peptide has the formula

X-LLLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCR-Z (SEQ ID NO: 268).

50. The method of Claim 17 wherein the peptide has the formula X-LLCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRT-Z (SEQ ID NO: 269).

51. The method of Claim 17 wherein the peptide has the formula X-LCLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTC-Z (SEQ ID NO: 270).

52. (new) The method of Claim 17 wherein the peptide has the formula X-CLIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTCM-Z (SEQ ID NO: 271).

53. The method of Claim 17 wherein the peptide has the formula X-LIFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTCMT-Z (SEQ ID NO: 272).

54. The method of Claim 17 wherein the peptide has the formula X-IFLLVLLDYQGMLPVCPLIPGSSTSTGPCRTCMTT-Z (SEQ ID NO: 273).

55. The method of Claim 17 wherein X is an acetyl group, and Z is an amido group.